REMARKS

This is in response to the official action of May 20, 2003. The points raised therein are addressed below in the order originally set forth.

Claims 1-3, 6-8, 14-16 and 29-31 stand objected to as informal in the use of a semicolon rather than a comma to separate phrases within the claim. The punctuation of the claims has accordingly been changed to utilize a comma rather than a semicolon, and it is respectfully submitted that this objection may be withdrawn.

Claims 1-3 stand rejected under the second paragraph of 35 USC 112 as lacking antecedent basis for "such therapy" as found in claim 1. Claim 1 has been corrected to clarify that "such therapy" is "said antineoplastic chemotherapeutic agent" and it is accordingly submitted that this rejection may now be withdrawn.

Claims 1-3, 6-8, 14-16 and 29-31 stand rejected under 35 USC 103(a) as obvious over Adams et al. in view of Gjerset. Reconsideration of this rejection is respectfully requested for the reasons set forth below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. *See* M.P.E.P. § 2143. First, the prior art reference or combination of references must teach or suggest all the claim limitations. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143. Here, it is respectfully submitted that there is not suggestion or motivation to combine the cited references, and not reasonable expectation of success for such a combination even if such suggestion or motivation were found.

Adams et al. describe proteasome inhibitors as NF-kB inhibitors, for reducing the rate of degredation of p53 protein, and for treating cell proliferative diseases such as cancer (column 6).

As acknowledged in the Official Action, Adams et al. do not teach administration of an anthracyclene antibiotic such as doxorubicin as a cytotoxic drug to be administered with a protesome inhibitor.

Gjerset concerns a treatment involving administration of p53 or p21 or MSH-2) in combination with an agent that inhibits DNA repair (column 2), and optionally further administering a DNA damaging agent such as doxorubicin (columns 2-3). Note that the p53 administered in Gjerset is an exogeneous p53, administered by means such as a p53 expression vector (see column 16, lines52-55). Gjerset utilizes exogenous p53 because he repeatedly emphasizes that he is concerned with cancers involving tumor cells lacking functional p53 (see, e.g., column 6, lines 5-9), as the p53 gene is "a frequent target of mutational inactivation in a wide variety of human tumors and is already documented to be the most frequently-mutated gene in common human cancers" (column 9, lines 34-38).

Given that the underlying theory of Gjerset is treatment of subjects in which endogeneous p53 is mutated to inactive form by replacement with an exogenous p53, there is no reason one of ordinary skill in the art would be suggested to or motivated to administer such a patient a proteasome inhibitor suggested by Adams to reduce the rate of degredation of endogeneous p53 protein, as Gjerset is concerned with the defectiveness of the endogeneous p53 in the first place. Nor could there be an expectation of success for such a combination, as Gjerset is replete with reference to the problem of mutated inactive endogeneous p53. Indeed, one skilled in the art would expect upregulation of endogeneous p53 as taught by Adams to dilute out any beneficial effect of administering an exogeneous p53 as taught by Gjerset.

Note that the present invention is based upon a different mechanism than the mechanisms taught in either Adams or Gjerset, and an advantage of the instant invention is that it would work whether p53 is functional in the host subject or not.

For the foregoing reasons, it is respectfully submitted that the present invention is not obvious over the cited references, and respectfully submitted that this rejection should be withdrawn.

Respectfully submitted,

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